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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/455,543	12/07/1999	STEVEN M. BESSETTE	45112-045	5289

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EXAMINER
PATTEN, PATRICIA A

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 11/05/2002 16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/455,543	Bessette et al.
Examiner	**Art Unit**
Patricia Patten	1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Oct 10, 2002*.

2a) [ ] This action is **FINAL**. 2b) [X] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1, 2, 5-14, and 16-28* is/are pending in the application.

4a) Of the above, claim(s) *17-28* is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *1, 2, 5-14, and 16* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [X] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) [ ] Interview Summary (PTO-413) Paper No(s). _____
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other:

DETAILED ACTION

Continued Prosecution Application

The request filed on 10/10/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/455,543 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 1-2, 5-14 and 16-28 are pending in the application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

Newly submitted claims 17-28 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Inventions I (Claims 1-2, 5-14 and 16) and II (Claims 17-28) are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and

they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions employ different constituents which would necessarily have a different effect when administered to an individual. For example, Invention I does not recite a cAMP inducer, while Invention II does, and thus the composition of Invention I is different from the composition of Invention II. The different inventions would be classified differently, and would impose a burdensome search on the Examiner.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 17-28 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Double Patenting

Claims 1-2, 5-14 and 16 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 09/455,544. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are all

drawn to a composition comprising a plant essential oil compound such as eugenol along with a signal transduction modulator such as cAMP.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The Office acknowledges that Applicants have confirmed [redacted] the Double Patenting rejection set forth in the Office Action dated 1/30/01. Applicants have relayed that a terminal disclaimer will be filed upon allowance, however, until that time, the rejection remains standing.

Claim Rejections - 35 USC § 112

Claims 1-2, 5-14 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a plant essential oil compound such as eugenol, along with a composition which was shown in the Instant specification to have growth inhibitory activity towards estrogen induced breast cancer cells (forskolin) does not reasonably provide enablement for any plant oil compound or any plant oil compound specifically recited in the Markush Group of plant essential oil compounds in Claim 1 in combination with a signal transduction modulator such as cAMP or cAMP-dependent protein kinase, tyrosine kinase, calcium

phospholipid-dependent protein kinase, mitogen activated protein kinase family members or calcium-calmodulin-dependent protein kinase for treating cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or

unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

First, Applicants have claimed a composition 'for treating cancer.' Although the Specification discloses data which appears to show a reduction in the occurance of cell proliferation with regard to estrogen induced human breast cancer cells *in-vitro* with specific compounds/combinations of compounds there is nowhere in the Specification which indicates that the product of the instant invention treated cancer would work *in-vivo*.

As the state of the art stands, treatments for cancer are rare: Bally et al. (US 5,595,756) stated that " Despite enormous investments of financial and human resources, no cure exists for a variety of diseases. For example, cancer remains one of the major causes of death. A number of bioactive agents have been found, to varying degrees, to be effective against tumor cells. However, the clinical use of such antitumor agents has been highly compromised because of treatment-limiting toxicities" (Col.1 lines 17-24).

There is grave unpredictability with regard to the *in-vitro* model as an appropriate cancer model *in-vivo* cancer efficacy. Inventions targeted for cancer treatment bear a heavy responsibility to provide supporting evidence because of this

unpredictability in biological responses to therapeutic treatments. The standard of enablement is higher for such inventions because as the state of the art stands, there is no 'prevention' or 'cure' for cancer ('756) and cancer treatments are rare. Thus, claims to treatments for cancer may be unbelievable in the absence of strong supporting evidence. There is no conclusive evidence in the Instant disclosure which indicates that the decreased occurance of breast cancer cells *in-vitro*, manifested from estrogen administration, would qualify as an acceptable model for cancers in other living creatures such as humans or bovine for example.

"The fundamental problem in drug discovery for cancer is that the model systems are not predictive at all.....attempts to use human cells in culture don't seem to be faring any better, partly because cell culture provides no information about whether a drug will make it to the tumor sites" (Gura, T. 1997). In the instant case, Applicants have failed to provide any xenograft of human cancer cell lines (or any other cancer cell cells) which have been manifested with estrogen. Thus, it is not clear if human breast cancer cells would be even relatively effected by the product (s) of the Instant invention *in-vivo*. Even mice which have been genetically engineered to produce colon cancer 'begin to diverge from those in human colon cancer, and the disease manifests itself differently as well. It spares the liver, for example, unlike the human cancer" (Gura, T). This is

conclusive evidence that the *in-vitro* model in the Instant case, cannot be reasonably extrapolated to treatment of cancer *in-vivo*.

It is noted that there in not a single example in the instant specification, working or prophetic, which indicates that the product of the Instant disclosure would perform beneficially on any type of cancer besides estrogen induced breast cancer cells *in-vitro*. Since there are **no** working examples, then one must consider the guidance provided by the instant specification and the prior art of record. It is noted that the instant claims encompasses a vast, almost limitless, number of cancers which could be treated, and yet the instant specification provides no working examples and no guidance that would permit the skilled artisan to practice the invention commensurate with the *scope* of the instant claims.

Claims drawn to pharmaceuticals and methods of treatment generally require supporting data because of the unpredictability in biological responses to therapeutic treatments. For the efficacy of a drug treatment in vivo faces unfavorable obstacles not present in in-vitro models. As such, ***in vivo utility necessarily involves unpredictability with respect to physiological activity of an asserted process in humans***. See discussion in Ex parte Kranz, 19 USPQ 2d 1216, 1218-1219 (6/90). For examples, drug delivery to the target area must survive the acidic environment of the stomach if administered orally. Additionally, the delivery of the drug across necessary cell surfaces in amounts needed to be efficacious, but not lethal to the subject,

necessitates sensitive testing in order to adequately determine the proper human dosage.

The high degree of unpredictability associated with the claimed method underscores the need to provide teachings in the specification that would provide the skilled artisan with specific treatment regimens that achieve a therapeutic benefit by *in vivo* or *ex vivo* gene therapy; however, the specification does not provide such guidance and fails to provide: correlation between inhibition of estrogen-induced breast cancer cell proliferation and a treatment for human cancers *in-vivo*, routes of delivery (e.g. intratumoral, intravenous etc.), dosage amounts/frequencies, and any other cancers besides the specific cancer which is manifested in human breast cancer cells subsequent to estrogen administration. Without such guidance in the specification and the lack of correlative working examples, the claims would ***require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan***.

In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

> "Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; ***however, he***

must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved." (emphasis added)

The instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v.*

Novo Nordisk A/S 42 USPQ2d 1001, at 1005). The claimed methods constitute such a "germ of an idea".

Thus, it would require undue trial and error experimentation, without a reasonable expectation of success for the skilled artisan to use the product of the Instant disclosure to treat cancer.

Second, Applicants have claimed compositions such as mitogen activated protein kinase family members admixed with plant essential oils such as thyme oil (which is one combination amongst a plethora of possible permutations). No such compositions are found within the Instant specification. The Examples, as presented on pp. 10-12 show that eugenol, forskolin, and a combination of eugenol (or thymol) and okadaic acid showed some decrease of estrogen induced/non-estrogen induced breast cancer cells. Applicant states that "...one or more signal transduction modulators may be used in combination with plant essential oil compounds and derivatives thereof to provide anti-proliferative, anti-estrogenic and/or anti-mitogenic compositions for prophylactically and/or therapeutically treating soft tissue cancers" (p.12 Instant specification). However,

this appears to be conjecture. The state of the art with regard to signal transduction modulators is highly unpredictable. It appears that Applicant has theorized that forskolin is representative of all 'signal transduction modulators' such as protein kinase and cAMP, however, has not provided any substantial evidence of a nexus between all 'signal transduction modulators' and inhibition of cancer cell proliferation *in-vitro*. Signal transduction within a living body is a highly complex cascade of reactions, of which many are not yet known. These cascades are highly regulated systems which involve many biochemical modulations and reactions. It is therefore highly unpredictable to ascertain whether any compound which 'modulates' signal transduction would display similar results to forskolin which has a specific reaction in the signal transduction pathway.

Additionally, as pointed out in a previous Office action, research has shown that **inhibitors** of protein kinases such as certain cAMP analogs as described by Clardiello et al. (1999) have a beneficial effect on abnormal cell proliferation (Please see pp. 821, where they discuss that PKAI is inhibited by the site selective cAMP analog 8-chloro-cAMP, which in turn induced growth inhibition *in vitro* and *in vivo*). Thus, the claims as instantly presented, appear to contradict the prior art. Compositions containing protein kinases and/or cAMP/cAMP dependent protein kinase complexes for decreasing cell proliferation were not found in the prior art. Because cell proliferation is a highly complex, unpredictable regulated system,

claims to a composition comprising a material such as a protein kinase which seems to contradict the prior art teachings, would necessarily need to provide clear, sufficient evidence within the Disclosure in order to substantiate such claims.

Accordingly, in the present instance, the claimed invention encompasses a veritable plethora of possible compounds of diverse structure and type and the use thereof as a pharmaceutical for treating cancer The inadequate disclosure coupled with a lack of representative examples and the art recognized unpredictability with respect to cancer treatment preclude the making and use of compounds within the scope of the presently claimed invention by the skilled artisan without undue experimentation.

Claims 1-2, 5-14 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The recitation of 'mitogen activated protein kinase members' (A) and growth factor receptor inhibitors' (B) is not enabled, as they have not been fully described within the Instant specification. What A and B compounds are Applicant referring to? There are no examples or structures of A or B in the

Instant specification. Lacking this critical information with regard to A and B, Applicants have failed to describe the invention so the skilled artisan would be able to reproduce the Instant invention without tedious trial and error protocol.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Patricia Patten, whose telephone number is (703)308-1189. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback is on 703-306-3220 The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Jon P. Weber, Ph.D.
Primary Examiner